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| 10/526,087 | 09/14/2005 | Henry H. Hsu | 30481/30002A | 6478 |

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| EXAMINER | |
|---|---|
| SEHARASEYON, JEGATHEESAN | |
| ART UNIT | PAPER NUMBER |
| 1647 | |
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| 03/17/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/526,087 | HSU, HENRY H. | |
| | Examiner | Art Unit | |
| | Jegatheesan Seharaseyon, Ph.D | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-11 are pending and under consideration.

### *Information Disclosure Statement*

2. The IDS submitted 2/13/2006 has been considered. Du et al. reference has not been considered because it is in a foreign language and no translation is provided.

### *Specification*

3. The use of the trademark Actimmune has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4a. Claims 1, 2 and 4-11 depending therefrom are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of fibrotic disease, does not reasonably provide enablement for prophylaxis of the fibrotic disease or the reduction in the incidence or severity of one or more side effects ordinarily associated with the administration of either drug alone in the treatment of the

fibrotic disease. The specification is also not enabling for the synergistic effects of the combination. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breath of claims. Ex Parte Forman, (230 USPQ 546 (Bd. Pat. App. & Int. 1986); In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 1 and 2 are drawn to the method of treatment or prophylaxis (prevention) of the fibrotic disease by administering a composition of IFN-γ and pirfenidone. Although, preamble does not recite “prophylaxis”, the claims clearly contemplate prophylaxis of the fibrotic diseases. However, specification (pages 31-32) and prior art only teach the treatment of fibrotic diseases by the administration of IFN-γ and pirfenidone. The specification as filed is insufficient to enable one of skilled in the art to practice the claimed invention for prophylaxis of the fibrotic diseases without an undue amount of experimentation because the specification and the prior art have not demonstrated the prophylaxis of the fibrotic diseases by administering composition of IFN-γ and pirfenidone.

Applicant has not disclosed how to use the claimed invention for prophylaxis of the fibrotic diseases by administering a combination of IFN-γ and pirfenidone to the subjects. There is insufficient evidence of the invention with respect to the *in vivo* operability of the claimed invention. Specifically, specification and prior art only teach the treatment of fibrotic disease and not the prophylaxis of fibrotic disease. For example, the specification fails to provide guidance with respect to what candidate population will be selected for the prophylaxis of fibrotic disease by administering a combination of IFN-γ and pirfenidone of the invention. There is no disclosure in the specification with respect to the dosages required to obtain prophylactic effect. It is also unclear for how long one would have to administer the medication. It is noted that if a patient population with the "disease symptoms" are identified, the onset of disease has taken place, thus the pathology cannot be prevented (only further progression maybe stopped).

Since, there is inadequate guidance as to the nature of the invention, it is merely an invitation to the artisan to use the current invention as a starting point for further experimentation for the prophylaxis of fibrotic diseases by administering the a combination of IFN-γ and pirfenidone of the invention. In addition, because there are no working examples provided describing prophylaxis of fibrotic diseases or models it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention.

In claim 1, Applicant is contemplating a synergistic effect of the combination of IFN-γ and pirfenidone for the treatment or prophylaxis. However, specification provides

no evidence for synergistic effects for the treatment or prophylaxis fibrotic diseases. Applicant has not provided the dosage required for producing a synergistic effect. The specification as filed is insufficient to enable one of skilled in the art to practice the claimed invention to produce a synergistic effect for the treatment or prophylaxis of the fibrotic disease without an undue amount of experimentation because the specification has not demonstrated the synergistic effect of the combination. Since, there is inadequate guidance as to the nature of the invention, it is merely an invitation to the artisan to use the current invention as a starting point for further experimentation for the treatment or prophylaxis of the fibrotic disease. In addition, because there are no working examples provided it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention.

In claim 2, Applicant is contemplating the reduction in the incidence or severity of one or more side effects ordinarily associated with the administration of either drug alone in the treatment of the fibrotic disease. It is not clear what dose of IFN-γ and pirfenidone will both treat the fibrotic disease and reduce the incidence or severity of one or more side effects ordinarily associated with the administration of either drug alone in the treatment of the fibrotic disease. The specification as filed is insufficient to enable one of skilled in the art to practice the claimed invention for the reduction in the incidence or severity of one or more side effects ordinarily associated with the administration of either drug alone in the treatment of the fibrotic disease without an undue amount of experimentation because the specification has not demonstrated the reduction in the incidence or severity of one or more side effects ordinarily associated

with the administration of either drug alone in the treatment of the fibrotic diseases. In fact the combination doses used in the instant invention for treatment of fibrotic disorders have been previously used individually or in combination for the treatment of fibrotic disorders Ziesche et al. (1999) and Ragu et al. (1999) both disclosed in PTO 1449 of 2/13/2006. Ziesche et al. disclose that the side effects of IFN-γ subsided within 9 to 12 weeks (p. 1264). Ragu et al. indicate that pirfenidone was well tolerated with minimal side effects which promptly subsided after discontinuation of the drug or decrease in dosage (p. 1066). Since, there is inadequate guidance as to the nature of the invention, it is merely an invitation to the artisan to use the current invention as a starting point for further experimentation for the reduction in the incidence or severity of one or more side effects ordinarily associated with the administration of either drug alone in the treatment of the fibrotic disease. In addition, because there are no working examples provided describing the reduction in the incidence or severity of side effects it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention.

Given the breadth of claims 1 and 2 in light of the unpredictability of the art as determined by the lack of working examples, the level of skill of the artisan, and the lack of guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention for the prophylaxis of the fibrotic diseases or the reduction in the incidence or severity of one or more side effects ordinarily associated with the administration of either drug alone in the treatment of the fibrotic disease by

administering a combination of IFN-γ and pirfenidone. Claims 4-11 are rejected insofar as they are dependent on rejected claims 1 and 2.

***Claim Rejections - 35 USC § 103***

5. following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5a. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ziesche et al. (1999, PTO 1449 of 2/13/2006) in view of Ragu et al. (1999, PTO 1449 of 2/13/2006).

The instant invention is drawn to a method of treating fibrosis in an individual by administering combination of IFN-γ and pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone).

Ziesche et al. (1999) teach the administering a combination of IFN-γ and prednisolone to treat idiopathic pulmonary fibrosis, a known fibrotic disease (p.1264).

The reference discloses the administration of 200 µg of FN-γ three times weekly and 50mg prednisolone daily (p.1264). Authors disclose that the lung function deteriorated in patients administered with prednisolone alone. In contrast, in the group receiving both IFN-γ and prednisolone the total lung capacity increased (see Fig. 1). Ziesche et al. also teaches the use of IFN-γ in the treatment of progressive pulmonary fibrosis including idiopathic pulmonary fibrosis, scleroderma and sarcoidosis. The reference teaches that the proliferation of fibroblasts and the accumulation of interstitial collagens are hallmarks of progressive organ fibrosis (p. 1264). It is disclosed that the side effects of IFN-γ such as fever, chills and muscle pain, subsided within the first 9 to 12 weeks (p. 1264). Ziesche et al. reference does not teach the use of IFN-γ and pirfenidone combination for the treatment fibrotic diseases.

Ragu et al. teach the use of pirfenidone to treat idiopathic pulmonary fibrosis. The reference teaches that pirfenidone is an antifibrotic drug (p. 1061).Ragu et al. discloses a dose of 40mg/kg/day up to a maximum of 3,600mg/day (p. 1062). Authors also indicate that pirfenidone was well tolerated with minimal side effects which promptly subsided after discontinuation of the drug or decrease in dosage (p. 1066). The reference also teaches that treatment with pirfenidone allowed discontinuation or tapering of prednisone and immunosuppressive therapy without further loss of lung function. Ragu et al. also disclose that IFN-γ has been demonstrated to inhibit lung fibroblast proliferation and collagen synthesis (p. 1068).

Therefore, it would have been *prima facie* obvious at the time of the invention to modify the treatment methods of Ziesche et al. (1999) to treat idiopathic pulmonary

fibrosis, a known fibrotic disease as taught by Ragu et al. (1999) using the therapeutic compositions of IFN-γ and pirfenidone combination. One of ordinary skill in the art would have been motivated to use the modified methods of Ziesche et al. to treat fibrosis including idiopathic pulmonary fibrosis by administering a combination of IFN-γ and pirfenidone (instead of using IFN-γ and prednisone) because Ragu et al. disclose that pirfenidone is an antifibrotic drug that is used in the treatment of fibrotic disease including idiopathic pulmonary fibrosis that has minimal side effects. Further, there is reasonable expectation of success because Ziesche et al. reference clearly teaches that the combination of IFN-γ and prednisone clearly produces a better clinical outcome compared to using prednisone alone. The rationale for using pirfenidone compared to prednisone is because pirfenidone is well tolerated with minimal side effects. One of ordinary skill in the art would have been motivated use the dosages used in Ziesche et al. and Ragu et al. because they are clinically effective. Although, liver fibrosis and cardiac fibrosis are not disclosed in Ziesche et al. and Ragu et al. because they share a common disease mechanisms with idiopathic pulmonary fibrosis (the proliferation of fibroblast and the accumulation of interstitial collagens) it would be *prima facie* obvious at the time of the invention to use the methods Ziesche et al. and Ragu et al. Therefore, the instant invention is *prima facie* obvious over Ziesche et al. (1999) and Ragu et al (1999).

6. No claims are allowable.

## Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon, Ph.D whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao, Ph. D can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JS
February 26, 2008

/Jegatheesan Seharaseyon/
Primary Examiner, Art Unit 1647